

Remarks

Claims 23, 36 and 37 are canceled herein. Applicants reserve the right to claim the subject matter of claims 23, 36 and 37 in continuing applications. Claims 19-22, 24-35 are pending in the application.

I. Priority

The Examiner asserts that prior-filed application No. 09/432,085 (the '085 application) fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. § 112 for one or more claims of the present application. (Office Action, page 3.) In particular, the Examiner asserts that “[t]he prior application does not disclose a negative selection marker and an antibiotic selection marker between a third and fourth recombination site on a vector with which an amplification production comprising a first and second recombination site is to be recombined.” Applicants respectfully disagree.

Support for a negative selection marker and an antibiotic selection marker can be found, *inter alia*, at page 15, line 16 through page 16, line 31 of the '085 application. In particular, page 16, lines 14-17 discloses toxic genes that may be used as negative selection markers. Support for the negative selection marker and the antibiotic selection marker being present between site-specific recombination sites can be found, *inter alia*, in Figures 7C and 8B of the '085 application. These Figures disclose a chloramphenicol resistance gene (CmR) adjacent to a *DpnI* gene and in between *attR1* and *attR3* recombination sites in the pEZC3101 and pEZC3501 plasmids. The same disclosure may also be found in prior-filed application No. 08/663,002 (now U.S. Patent No. 5,888,732), filed June 6, 1996. Further disclosure of how negative selection markers may be used to select molecules resulting from site specific recombination mediated exchange of nucleic acid segments can be found at page 17, lines 6-15 of priority application 08/486,139, filed June 7, 1995 (the '139 application).

As amended herein, claim 19 is directed in part to “a vector comprising, in order, a third recombination site, a negative selection marker, and a fourth recombination site.” Applicants believe that the disclosure of the '139 application fully supports all of the

limitations of claim 19 as required by the first paragraph of 35 U.S.C. § 112 and that claim 19 is entitled to a priority of June 7, 1995.

II. Rejection of the Claims Under 35 U.S.C. §§ 102(e) and 103(a)

Claims 19-30 and 32-37 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Johnson *et al.* (WO 93/19172) in view of Bernard (*BioTechniques* 21:320-323 (1996)). (Office Action, page 4.)

Claims 19-30 and 32-37 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Griffiths *et al.* (U.S. Patent No. 5,962,255). (Office Action, page 6.)

Claims 19-30 and 32-37 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Johnson *et al.* (WO 93/19172) in view of Bernard *et al.* (U.S. Patent No. 5,910,438). (Office Action, page 8.)

Claims 19-30 and 32-37 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Griffiths *et al.* (U.S. Patent No. 5,962,255) in view of Bernard *et al.* (U.S. Patent No. 5,910,438). (Office Action, page 9.)

Applicants respectfully disagree with these rejections.

The Examiner asserts that by combining the disclosures of Johnson *et al.* and Griffiths *et al.* with Bernard and Bernard *et al.*, one of skill in the art would arrive at the presently claimed invention. (Office Action, pages 4 and 6.) The U.S. Supreme Court recently noted that:

A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, *it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.* This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

(*KSR Int'l v. Teleflex Inc.*, 550 U.S. at ___, Slip Op. at 1-24 (Apr. 30, 2007) (No. 04-1350) (emphasis added).) Thus, the U.S. Supreme Court has provided guidance for assessing whether an invention is obvious and has indicated that merely collecting “building blocks”

does not provide a reason that would prompt one of skill in the art to arrive at the claimed invention.

The Examiner cites Bernard as providing disclosure of the use of negative selection markers for the selection of plasmids where the desired insertion of a nucleic acid segment has occurred. (Office Action, pages 4 and 6.) Further, the Examiner states that "the use of antibiotic resistance and negative selection markers on plasmids is well known in the art, as taught by Bernard." it was well known in the art to include such selection markers in DNA molecules in order to select for the presence or absence of a DNA molecules of interest, as taught by Bernard." (Office Action , page 5.) As explained below, in view of the language of pending claim 19, this statement is not directly on point.

As exemplified in part by Figure 1, Bernard and Bernard *et al.* describes a selection vector and associated system which involves the insertion of nucleic acid into the vector at a site which encodes a toxic fusion protein. This insertion results in insertional inactivation of the toxic fusion protein coding region.¹

A method of exchanging nucleic acid segments using site-specific recombination sites is illustrated in Figure 1 of the captioned application. In this method, in the presence of recombinase proteins, nucleic acid segments A and C are exchanged so that segment A becomes associated with segment D and segment C becomes associated with segment B. In this method, the mechanism employed is an exchange of nucleic acid segments between nucleic acid molecules. Selectable markers, such as negative selection markers and antibiotic resistance genes, may be used to select for the desired nucleic acid molecules both before and after the exchange has taken place (as described in the section entitled "Selection Scheme" on pages 16-17 of the '139 application). For example, the combination of an antibiotic resistance gene and a negative selection marker may be used to apply selective pressure (1) in favor of nucleic acid molecules which contain a nucleic acid segment that contains this gene (*e.g.*, a nucleic acid molecules which contains a segment comprising "a third recombination site, a

¹ As already noted, it is Applicants position that the claims presented herein are entitled to the priority date of prior-filed application No. 08/486,139, filed June 7, 1995. Thus, Bernard (*BioTechniques*) is not prior art to the pending claims under 35 U.S.C. § 102(b). However, several U.S. patents disclose technology similar to that of Bernard. Two of these patents, U.S. Patent Nos. 6,180,407 and 7,176,029, have previously been cited by Applicants.

negative selection marker, and a fourth recombination site") and (2) against nucleic acid molecules that contain the negative selective marker (*e.g.*, nucleic acid molecules which were intended to become involved in nucleic acid segment exchange but failed to participate).

With respect to claim 19 presented herein, a segment of a vector is exchanged with an amplification product. As noted above, the disclosures of Bernard describe the insertion of nucleic acid segments rather than exchange of nucleic acid segments. In other words, as would be appreciated by one skilled in the art, insertional inactivation (Bernard and Bernard *et al.*) is a very different process than cassette excision (claim 19). Applicants therefore assert that none of the art cited by the Examiner would lead one skilled in the art to methods defined by the pending claims. In particular, Applicants assert that one skilled in the art, reviewing the art cited by the Examiner would not arrive at a method for cloning an amplification product involving the use of "a vector comprising, in order, a third recombination site, a negative selection marker, and a fourth recombination site, wherein the third and fourth recombination sites do not recombine with each other. . . ."

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 103(b).

III. Double Patenting

Claims 19 and 22-37 stand rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 29-34 of U.S. Patent No. 5,888,732. (Office Action, page 7.) Claims 19-37 stand rejected on the grounds of non-statutory obviousness-type double patenting as being unpatentable over claims 15-20 and 45-55 of U.S. Patent No. 6,720,140. (Office Action, page 7.)

Applicants defer responding to this rejection until patentable subject matter has been determined at which time Applicants will consider whether a terminal disclaimer is needed.

IV. Rejection of the Claims under 35 U.S.C. § 112, second paragraph

Claims 19-37 stand rejected as being indefinite for failing to particularly point and distinctly claim the subject matter which applicant regards as the invention. (Office Action, page 12.) Applicants respectfully disagree.

The Examiner asserts that it is unclear which molecules are referred to by the phrase “the third and fourth recombination sites do not recombine with each other.” (Office Action, page 12.) Applicants believe that the language of the claim makes it clear that the third and fourth recombination sites are part of the vector but, in order to advance prosecution, Applicants have amended claim 19 to insert the phrase “of the vector” to make this point explicitly clear.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, second paragraph.

Conclusion

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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